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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/591,789	06/12/2000	John J. Machalonis	7760-012	5233

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EXAMINER

PARKIN, JEFFREY S

ART UNIT PAPER NUMBER

1648

DATE MAILED: 11/05/2002

8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicati n No.

09/591,789

Applicant(s)

MACHALONIS ET AL.

Examiner

Jeffrey S. Parkin, Ph.D.

Art Unit

1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 03 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 August 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 7, 24 and 25 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 7, 24, and 25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application)
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

Response to Amendment

Status of the Claims

1. Acknowledgement is hereby made of receipt and entry of the response filed 15 August, 2002, wherein claims 1-6 and 8-23 were canceled without prejudice or disclaimer and claims 7, 24, and 25 amended. Claims 7, 24, and 25 are currently under examination.

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Claim Objections

2. The previous objection to claims 7, 24, and 25 because of various informalities is hereby withdrawn in response to Applicants' amendment.

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35 U.S.C. § 112, First Paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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4. Amended claims 7, 24, and 25 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed toward a method for increasing T_H1 cytokine production while decreasing T_H2 cytokine production through the administration of a peptide having SEQ ID NO.: 1 or derivatives thereof. The purpose of this modulation is to prevent and/or treat cardiovascular disease, allergic disorders, solid tumors, and the progression to AIDS in an HIV-positive patient (see specification,

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first paragraph, p.1). The invention appears to be predicated upon the assumption that these various pathologies can be treated by shifting the immune state of a patient from that of a T_H2 state, which is generally associated with phagocyte-independent immune responses (i.e., IgE production, IgG production, mast cell activation and differentiation), to one of a T_H1 state, which is generally associated with phagocyte-dependent immune responses (i.e., delayed-type hypersensitivity, production of opsonizing antibodies, production of complement-fixing antibodies).

As previously set forth, the legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure still fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide adequate guidance pertaining to the molecular determinants modulating the favorable immunological properties and activities of the claimed peptide. The claimed invention involves the administration of a T-cell receptor (TCR) peptide to the patient. The TCR is a heterodimeric cell surface protein comprising an α and β polypeptide that is normally involved in a number of immunological responses such as antigen recognition (Davis and Chien, 1999). The TCR recognizes antigenic peptides presented in the context of MHC class I or II. Each α and β

subunit is glycosylated and has a molecular weight of 40,000-50,000. TCRs are quite diverse and share structural similarities with immunoglobulins including variable, constant, and joining regions. Thus, they are quite complex molecules. However, the disclosure fails to provide any guidance pertaining to the location of the TCR peptide within the context of the larger receptor. Thus, it is not readily manifest how the administration of this peptide will modulate the immune response in favor of T_H1 -type responses. The disclosure fails to provide any guidance pertaining to the biochemical and immunological activities of the claimed peptide (i.e., agonist or antagonist). For instance, does the peptide act by inhibiting TCR interactions on $CD4^+$ T-lymphocytes or does it function in some other manner. How will the skilled artisan keep the peptide from interfering with all normal TCR interactions on both $CD4^+$ and $CD8^+$ T-lymphocytes? What will preclude the patient from developing an immune response against the peptide of interest thereby leading to aberrant immunological activity (i.e., down-modulation of TCR-mediated immune responses)?

Applicants traverse and submit that there this no legal requirement that a knowledge of the underlying mechanism of action be understood. While there is no explicit legal requirement that the mechanism of action be partially or completely understood, nevertheless, in claims that are extremely broad and encompass numerous species (i.e., any derivative of SEQ ID NO.: 1) or are directed toward arts that are extremely unpredictable (i.e., the of immunotherapeutic strategies to treat cancer, cardiovascular disorders, and infectious diseases) the identification of such information would help the skilled artisan make a reasonable determination as to whether or not the claimed invention would be expected to function in the manner claimed. In this particular application, the absence of a better understanding of the mechanisms underlying the therapeutic properties of the peptides of interest are certainly a short-coming. For instance, the skilled

artisan cannot reasonably predict which peptidic derivatives will have the desired properties since the specification fails to provide any guidance pertaining to the molecular determinants modulating these activities.

5 Moreover, the Examiner raised a number of legitimate scientific issues that were ignored in the response. For instance, the following items were raised: (i) the disclosure fails to provide any guidance pertaining to the location of the TCR peptide within the context of the larger receptor; (ii) it is not readily manifest
10 how the administration of this peptide will modulate the immune response in favor of T_H1 -type responses; (iii) the disclosure fails to provide any guidance pertaining to the biochemical and immunological activities of the claimed peptide (i.e., agonist or antagonist); (iv) it is not readily manifest how the skilled
15 artisan will keep the peptide of interest from interfering with normal TCR interactions on both $CD4^+$ and $CD8^+$ T-lymphocytes; (v) it is not readily manifest what will preclude the patient from developing an immune response against the peptide of interest thereby leading to aberrant immunological activity (i.e., down-
20 modulation of TCR-mediated immune responses). None of these concerns were addressed in the reply.

2) The disclosure fails to teach that modulating T_H1/T_H2 cytokine levels will have any ameliorative or therapeutic effect in cardiovascular disease, allergic disorders, solid tumors, or the
25 progression to AIDS. The correlates of protective immunity for many disorders remain to be elucidated. Moreover, many pathogens and disease states fail to elicit a simple T_H1 or T_H2 phenotype (Graziosi et al., 1994; Maggi et al., 1994; Romagnani et al., 1994; Shearer and Clerici, 1992). For instance, it is not clear what
30 type of immune responses will protect against solid tumors, allergic disorders, cardiovascular disease, or the progression to AIDS. In some situations, both humoral and cell-mediated immune responses may be required. Thus, the interplay between " T_H1/T_H2 "

cytokine responses may not be so simple. In fact, what is more likely to required, is a balance between the two responses to favorably eliminate tumors and HIV. It is not readily manifest how the peptide of interest would facilitate the treatment of cardiovascular disease. For instance, would the peptide be capable of inducing immune responses that remove plaque from clogged arteries? What type of allergic disorders could the peptide of interest prevent or treat? Absent sufficient guidance from the disclosure, the skilled artisan has been extended an undue invitation to further experimentation.

In response to these concerns, Applicants contend that the issues raised by the Examiner are directed toward a lack of utility and should be addressed under the Utility Guidelines (M.P.E.P. § 2107). Applicants note that all that is required under these guidelines is that a "reasonable" correlation between the effectiveness of the methods and asserted use be provided. These arguments are completely misdirected. The crux of this aspect of the rejection is clearly directed toward the ability of a TCR peptide to modulate T_H1/T_H2 cytokine levels in such a manner that it can reasonably be expected to have some sort of ameliorative or therapeutic effect in cardiovascular disease, allergic disorders, solid tumors, or the progression to AIDS. Applicants are reminded that the present rejection is based solely upon those tenets governing 35 U.S.C. § 112, first paragraph, rejections. This is not a rejection based upon 35 U.S.C. § 101. Rejections made under 35 U.S.C. § 112, first paragraph, address different issues from those examined under the utility guidelines. These issues include whether the claims are fully supported by the disclosure (*In re Vaeck*, 947 F.2d 488, 495, 20 U.S.P.Q.2d 1438, 1444 (Fed. Cir. 1991)), whether the applicant has provided an enabling disclosure of the claimed subject matter (*In re Wright*, 999 F.2d 1557, 1561-1562, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993)), and whether the

applicant has provided an adequate written description of the invention (*Chemcast Corp. v. Arco Industries Corp.*, 913 F.2d 923, 927-928, 16 U.S.P.Q.2d 1033, 1036-1037 (Fed. Cir. 1990)). The preceding paragraph raised a number of legitimate scientific concerns which were ignored in the response. Applicants are invited to provide any data or publications that suggest that the administration of a TCR peptide can reasonably be expected to protect against solid tumors, allergic disorders, cardiovascular disease, or the progression to AIDS.

3) The disclosure fails to provide any working embodiments. The disclosure fails to provide any relevant models of tumor progression, cardiovascular disease, allergic disorders, or HIV infection. The disclosure fails to provide any data involving the claimed peptide demonstrating that it can effectively treat tumor development, AIDS progression, cardiovascular disease, or sundry allergic disorders. The development of any given therapeutic is a difficult process involving testing of the peptide or compound of interest in *in vitro* tissue culture assays, *in vivo* animal models, and finally in preliminary clinical studies. Only by performing such studies can the skilled artisan reasonably conclude that such compounds will be efficacious (Öberg and Vrang, 1990; Gait and Karn, 1995; Yarchoan and Broder, 1992). However, the disclosure fails to provide suitable evidence in support of the claimed activity of the TCR peptide.

Applicants reply and submit that there is no legal requirement that working embodiments be provided. Once again, while there may be no explicit requirement for such embodiments, nevertheless, in complex biotechnology applications, such as the instant one, the inclusion of working embodiments would facilitate the determination of enablement under 35 U.S.C. § 112, first paragraph. The failure to have any working embodiments suggests that Applicants have not been able to demonstrate that the claimed invention functions as

claimed. Applicants are also directed to *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986), wherein the courts clearly noted that the presence or absence of working examples was an important consideration in making enablement determinations under this statute. Applicants are invited to provide any data demonstrating that the claimed TCR peptide, or derivatives thereof, were capable of modulating immune response in the desired manner.

4) As discussed *supra*, the prior art is unpredictable and teaches that the development of efficacious treatments for cardiovascular disease, allergic disorders, solid tumors, and antivirals is an arduous and often unsuccessful undertaking (Graziosi et al., 1994; Maggi et al., 1994; Romagnani et al., 1994; Shearer and Clerici, 1992; Öberg and Vrang, 1990; Gait and Karn, 1995; Yarchoan and Broder, 1992). Moreover, the complexity of the TCR and the various roles it plays in T-cell signaling make it difficult to identify and predict which compounds will prove useful as therapeutic agents (Evavold et al., 1993; Madrenas et al., 1996). Perusal of the disclosure fails to provide any evidence that would lead the skilled artisan to conclude otherwise. Applicants' response failed to address this concern.

5) The claims are of considerable breadth and remain unsupported by the disclosure. The claims encompass the treatment of any solid tumor, any cardiovascular disorder, any allergic disorder, and the progression to AIDS, employing the claimed TCR receptor peptide, or any derivative thereof. As noted above, the disclosure fails to provide support for any of these claims. The first paragraph of § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification. *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970). *In re Vaeck*, 20 U.S.P.Q.2d 1438 (C.A.F.C. 1991). *In re Angstadt*, 537 F.2d 498, 502-03, 190 U.S.P.Q. 214, 218

(C.C.P.A. 1976). Clearly the inventors have not met their obligation under this section.

Applicants appear to contend once again that the issues raised by the Examiner are directed toward a lack of utility and should be addressed under the Utility Guidelines (M.P.E.P. § 2107). Once again this argument is completely misdirected. The crux of this aspect of the rejection is clearly directed toward the breadth of the claimed invention. Applicants are attempting to modulate T_H1/T_H2 cytokine responses through the administration of a TCR peptide, or derivative thereof, in such a manner that it can reasonably be expected to have some sort of ameliorative or therapeutic effect in cardiovascular disease, allergic disorders, solid tumors, or the progression to AIDS. Apparently Applicants' representative does not understand or appreciate the breadth of the claimed invention. These four areas encompass a large number of complex and diverse disorders. Many of these pathologies involve fundamentally different, but complex, mechanisms of action. Moreover, the claims encompass the administration of a large genus of TCR peptide derivatives whose properties are completely unknown. Applicants are again reminded that the present rejection is based solely upon those tenets governing 35 U.S.C. § 112, first paragraph, rejections. This is not a rejection based upon 35 U.S.C. § 101. Rejections made under 35 U.S.C. § 112, first paragraph, address different issues from those examined under the utility guidelines. These issues include whether the claims are fully supported by the disclosure (*In re Vaeck*, 947 F.2d 488, 495, 20 U.S.P.Q.2d 1438, 1444 (Fed. Cir. 1991)), whether the applicant has provided an enabling disclosure of the claimed subject matter (*In re Wright*, 999 F.2d 1557, 1561-1562, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993)), and whether the applicant has provided an adequate written description of the invention (*Chemcast Corp. v. Arco Industries Corp.*, 913 F.2d 923, 927-928, 16 U.S.P.Q.2d 1033,

1036-1037 (Fed. Cir. 1990)).

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation to practice the claimed invention.

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Finality of Office Action

5. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET
10 TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY
15 ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

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Correspondence

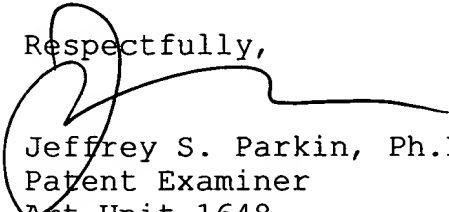
6. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be
25 directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate
30 their expeditious processing and entry.

7. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from
35 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, James Housel or Laurie Scheiner, can be

Serial No.: 09/591,789
Applicants: Marchalonis, J. J., et al.


reached at (703) 308-4027 or (703) 308-1122, respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,



Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

31 October, 2002



JAMES HOUSEL 11/4/02
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600